Trial protocol

The trial protocol was submitted to UNSW ethics committee on Nov 29, 2015, prior to randomisation of the first participant.

The Statistical Analysis Plan was drafted on Mar 2, 2020.

One major change was made to the trial protocol during the trial.

June 2016 – due to error in the specification of repeated measures used for the sample size calculation the sample size was changed to 276 and disability, measured by the RMDQ, from primary to secondary outcome. This change was included in the published protocol (Bagg et al. 2017) and submission to ethics committee on Nov 27, 2016.

The RESOLVE Trial (NHMRC1087045): Informed Sensorimotor Retraining for Chronic Low Back Pain

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RESEARCH PROBLEM AND ITS SIGNIFICANCE

Low Back Pain (LBP) is the leading cause of disability worldwide (Balagué et al., 2011; Vos et al., 2012). Most people recover from an acute episode quickly, with a 58% reduction in pain and disability and 82% return-to-work at 4 weeks (Pengel et al., 2003), however residual symptoms have been reported to persist for up to five years (Enthoven et al., 2004). The incidence of chronic low back pain (CLBP) following an acute episode ranges from 5-20% (Koes et al., 2006; Mehling, 2012; Pengel et al., 2003). This number appears to have increased over the previous twenty years (Freburger, 2009; Martin, 2008) based on United States data. In Australia, as many as 40% of people will develop CLBP from an acute episode of LBP (Henschke et al., 2008). The CLBP cohort is more difficult to treat, takes longer to recover (Costa et al., 2009; Menezes et al., 2012) and incurs the greatest costs (Walker et al., 2003).

The major problem with treatment of CLBP is that patients' primary concern is obtaining pain relief (Hush et al., 2009) and complete recovery appears to be primarily mediated by recovery from pain (Henschke et al., 2008). We know that, unfortunately, contemporary treatments are minimally effective (Machado et al., 2008) at achieving pain relief. Best-practice advocated (Koes et al., 2010) graded activity exercise has no more effect than motor-control exercise (Macedo et al., 2012), which is only slightly more effective than placebo at improving global function but not pain (Costa et al., 2009). Clearly, worthwhile reductions in pain are not being achieved and this is contributing to the slow recovery and economic burden of the CLBP population.

A new approach to chronic pain management has been conceptualised in the cortical body-matrix. The cortical body-matrix has been proposed as an expression of the coordinated drive by a network of brain structures to maintain homeostatic and psychological integrity when there is perturbation to body structure and orientation (Moseley et al., 2012a). There is compelling evidence that brain structures within the cortical body-matrix are disrupted in patients with CLBP (Bowering et al., 2014; de Lussanet et al., 2012; Luomajoki & Moseley, 2011; Moseley et al., 2008a, b, 2012b; O'Sullivan et al., 2013; Tsao et al., 2008; Wand et al., 2010, 2013a, b; Willigenburg et al., 2013). Targeting the function of these brain structures using specific therapeutic interventions in complex regional pain syndrome and phantom limb pain has produced significant reductions in pain. (Bowering et al., 2013; Cacchio et al., 2009; Chan et al., 2007; Flor et al., 2001; Moseley et al., 2008a; Moseley & Wiech, 2009). It would appear that employing the same interventions in the CLBP cohort might produce similar treatment effects.

This hypothesis is supported by promising pilot data. Several interventions for targeting the psychophysical disturbances observed in CLBP, as well as pain biology education (Clarke et al., 2011; Gallagher et al., 2013; Louw et al., 2011; Moseley et al., 2004) have, in all cases, produced significant reductions in pain intensity in patients with CLBP (Trapp et al., 2014; Wand et al., 2011, 2012, 2013; Wälti et al., 2015). Targeting the brain structures represented by the cortical body-matrix, in complement to education and functional movement training may constitute the new approach needed to achieve pain relief for CLBP sufferers. Accordingly, Informed Sensorimotor Retraining represents a truly biopsychosocial approach to rehabilitation of people with CLBP.

AIMS

The RESOLVE trial will investigate the effect of Informed Sensorimotor Retraining versus placebo control on pain intensity and disability in a large two-group randomised, controlled clinical trial of people with CLBP.
We hypothesise that Informed Sensorimotor Retraining will produce clinically meaningful reductions in pain intensity and disability versus placebo control at six weeks post intervention for people with CLBP.

RESEARCH PLAN

Study type

Two-group, participant blinded, randomised controlled clinical trial with repeated measures comparison of means

Setting/Location

Recruitment: Community-based advertisement and primary care practices, greater Sydney area, NSW, Australia
Enrolment, intervention and assessment: Neuroscience Research Australia (NeuRA), Barker Street, Randwick, Sydney NSW 2031, Australia

Duration of Study
September 2015 – September 2019

METHODS
Participants
Inclusion Criteria

- Primary complaint of pain in the area between the 12th rib and buttock crease with or without accompanying leg pain
- Low back pain of at least 12 weeks duration
- Mean pain intensity Numerical Rating Scale (NRS) ≥ 3/10 in the past week
- Sufficient fluency in the English language to understand and respond to English language questionnaires and to engage with the intervention
- Partner (friend or spouse) who is able to assist with part of the intervention
- Internet access
- Age 18-70, inclusive

Exclusion Criteria

- New onset of low back pain preceded by at least one year free from low back pain (recurrence)
- Known or suspected serious spinal pathology (fracture; malignant, inflammatory or infective diseases of the spine; cauda equina syndrome or widespread neurological disorder)
- Suspected or confirmed pregnancy or less than six months post-partum
- Nerve root compromise (any two of altered strength, reflex or sensation for the same nerve root)
- Spinal surgery less than twelve months previously
- Scheduled for major surgery during the treatment or follow-up period
- Uncontrolled mental health condition (eg, schizophrenia, bipolar disorder, major depressive disorder) that precludes successful participation
- Any of the contraindications to transcranial direct current stimulation (Constantinescu et al., 2010), cranial electrical stimulation, short wave diathermy (Shields et al., 2002) or low intensity laser therapy (DJO Global, n.d.)

Procedures
Recruitment
Primary care practitioners will identify potentially suitable participants during their consultation or participants will be exposed to community-based advertisement about the trial. In either case, the potential participant will contact the research team via telephone or email. A study researcher will explain the study protocol and eligibility criteria to the potential participant and with verbal consent, assess the potential participant for study eligibility over the telephone. Potential participants who are eligible to participate in the trial will be provided with the participant information statement and consent form (PICF) via email or post. They will have at least 24 hours opportunity to read the PICF. If the potential participant is eligible and remains interested, they will be invited to a baseline session. During the baseline session, one of the researchers will review the study protocol, confirm eligibility with respect to the inclusion and exclusion criteria, and obtain written informed consent. Baseline outcome data will also be collected during this session, following which the patient will be randomised.

Treatment Intervention
Participants randomised into the treatment intervention group will receive a twelve week program of Informed Sensorimotor Retraining. Informed Sensorimotor Retraining includes; pain biology education, sensory training, motor training and functional movement training. The pain biology education will take place during two 45-60min sessions over the first two weeks and in 20min doses over the ensuing ten weeks. The therapist will identify key unhelpful beliefs about the nature of low back pain that require restructuring (change). Restructuring techniques targeted to each patient will commence as part of the pain biology education and continue throughout the intervention.
From the second week, participants will commence sensory and motor training. The sensory training involves tactile localisation, discrimination and graphaesthesia over the lower back. The motor training involves left-right recognition training and motor imagery.
From week six, participants will engage in a 7-week program of feedback enhanced functional movement training. This is stratified to target the functional limitations of the individual and is performed with mirror-visual and other forms of feedback. All of the training will be delivered in a progressive graded fashion as part of 60min sessions (one per week) with the study therapist and in the form of home training, totalling 30mins per day, seven days per week.
The study therapist will monitor participant achievement of key learning targets of the pain biology education and progress with restructuring of cognitive barriers.

Participant progress through the treatment paradigm will be directed using a standard progression protocol. Participants are free to progress ahead of schedule provided they meet key progression criteria for each stage of the paradigm.
Participants will not be required to stop any current treatment for their low back pain.

Control Group Intervention
Participants randomised into the control group intervention will receive a graded program of sham/placebo interventions, matched to the time and therapist interaction of the treatment intervention. Sham pain biology education will be delivered during two 45-60min sessions over the first two weeks and in 20min doses over the ensuing ten weeks. Participants will be invited to discuss their current and past treatments. The study therapist will not provide advice about their low back pain. From week 2, participants will commence a progressive program of sham transcranial direct current stimulation (tDCS), detuned cranial electrical stimulation, detuned short-wave diathermy and detuned low intensity laser therapy, delivered during one 60 min session per week over 11 weeks.
Participants will not be required to stop any current treatment for their low back pain.

Randomisation
A trial researcher not involved in patient recruitment or data collection will create a randomisation schedule using randomisation software. The schedule will be used to create 266 consecutively numbered, sealed, opaque envelopes containing allocations.

Blinding
Patients will be blinded to group allocation and study hypothesis. It is not possible for therapists to be blinded to the study hypothesis as the treating therapists are on the research team. The statistician analysing the data will be blind to group allocation.

Sample Size Calculations
We require 266 patients to detect a one point (SD=2.5) between group difference in the first primary outcome, pain intensity (Numerical Rating Scale), at six weeks post intervention. We consider this to be the smallest worthwhile effects that would justify implementation of the intervention. A one point on the NRS is established as the minimal clinically important difference for pain intensity in chronic pain clinical trials (Dworkin et al., 2008).
Sample size was calculated using the Glimmpse software. We calculated for 7 repeated observations, an estimated intra-cluster correlation (correlation between the observations) with base 0.6 and decay rate 0.1, Type I error (alpha) of 5% and allowing for up to 15% loss to follow up. We conservatively ignored the increase in statistical power conferred by baseline covariates and stratification.

Outcomes
The primary outcomes will be pain intensity (Numerical Rating Scale) and Disability (Roland Morris Disability Questionnaire) at six weeks post intervention.
Secondary outcomes will include two-point discrimination distance, left-right recognition accuracy, depression subscale of the Depression, Anxiety and Stress Scale (DASS-21), Pain Catastrophising Scale, credibility and expectancy questionnaire, Neurophysiology of Pain questionnaire, Back Beliefs Questionnaire, Fremantle Back Awareness Questionnaire, Tampa Scale of Kinesophobia, Pain Self-Efficacy Questionnaire, Insomnia Severity Index, EuroQoL 5D-5L, Movement Imagery Questionnaire-Revised, Health Resource Use and Usual Activities, Elgueta-Cancino Pelvic Tilt Test. A measure of recurrence will be taken at 52 weeks for patients who are pain free for a month or longer.
Participants will be assessed in all measures at baseline, 3 and 6 weeks of the intervention, immediately post-intervention (week 12) and at 6 weeks, 3, 6 and 12 months post-intervention. All questionnaires will be accessible via secure web-links emailed to patients individually. Tactile acuity will be assessed using two-point discrimination by the study therapists. The Recognise® software provides left-right recognition accuracy and response time data. Individual participant data will be extracted into a spreadsheet using software.

Data and treatment integrity
Trial data integrity will be monitored by regularly scrutinising data files for omissions and errors. All data will be double entered and the source of any inconsistencies will be explored and resolved. Electronic data will be stored on password-protected servers at NeuRA and paper-form data stored in locked filing cabinets at NeuRA. De-identified data will be stored in separate files/cabinets to those containing participant details and trial identification numbers.
Treatment adherence will be determined by recording attendance at treatment sessions and by analysing participant activity diaries. The Recognise® software will also be used to track adherence to the laterality recognition component of the treatment intervention.

Statistical Analysis

The data will be analysed by intention-to-treat by a statistician blinded to group allocation. We will analyse the effect of the treatment intervention separately for each outcome using linear mixed models with random intercepts for individuals to account for correlation of repeated measures. The model will include terms for important prognostic factors measured prior to randomisation and specified a priori. We will obtain estimates of the effect of the intervention and 95% confidence intervals by constructing linear contrasts to compare the adjusted mean change (continuous variables) or difference in proportions (dichotomous variables) in outcome from baseline to each time point between the treatment and control group. Linear contrasts will be used to determine the effect of Informed Sensorimotor Retraining compared to placebo control.

SIGNIFICANCE

There is currently pilot data from one clinical trial (Wälti et al., 2015) and one clinical case-series (Wand et al., 2011) that a central nervous system training approach will produce a beneficial reduction of pain in people with CLBP. Furthermore, there is also evidence of independent effect of several treatment techniques for targeting central nervous system processes and outputs (Trapp et al., 2014; Wand et al., 2012, 2013a). This will be the first large-scale assessment of Informed Sensorimotor Retraining beyond the pilot stage. This trial will tell us whether treatments that target the function of the central nervous system are more effective than placebo in a large, representative group of people with CLBP. The trial will also demonstrate whether a paradigm of treatment delivery that is sequential, inter-related and feeds forward, in-line with current understanding of central nervous system physiology and the biopsychosocial model, produces a beneficial reduction in pain for people with CLBP.

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The RESOLVE Trial for people with chronic low back pain: statistical analysis plan

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Declarations of interest

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Abstract

Background: Statistical analysis plans describe the planned data management and analysis for clinical trials. This supports transparent reporting and interpretation of clinical trial results. This paper reports the statistical analysis plan for the RESOLVE clinical trial. The RESOLVE trial assigned participants with chronic low back pain to graded sensory-motor precision training or sham-control.
Results: We report the planned data management and analysis for the primary and secondary outcomes. The primary outcome is pain intensity at 18-weeks post randomisation. We will use mixed-effects models to analyse the primary and secondary outcomes by intention-to-treat. We will report adverse effects in full. We also describe analyses if there is non-adherence to the interventions, data management procedures and our planned reporting of results.
Conclusion: This statistical analysis plan will minimise the potential for bias in the analysis and reporting of results from the RESOLVE trial.
Administrative information:
Funding: This work was funded by the National Health and Medical Research Council (NHMRC) of Australia, ID1087045
Ethics: University of New South Wales HREC (HC15357)
Trial registration: ACTRN12615000610538
Trial protocol: Bagg et al. (2017) *J Physio*, doi:10.1016/j.jphys.2016.11.001
SAP version: 2 Mar 2020

Keywords

Back pain (MeSH), chronic pain (MeSH), statistical data analysis (MeSH), clinical trial (MeSH)

Introduction

Background and rationale

Low back pain is a burdensome and disabling health condition.[1,2] People who experience low back pain for longer than three months have a low chance of recovery and experience substantial functional and financial difficulty.[3–10] Results of clinical trials of contemporary interventions indicate that, on average, people with persistent low back pain experience small to no benefit, compared to control. Accordingly, there is an urgent need to develop more effective interventions.

Recent progress in understanding the role of the central nervous system (CNS) in the low back pain experience bears promise for the development of new treatment approaches. Accumulating data indicate that people with persistent low back pain have differences in CNS structure, function, and biochemistry; compared to people without pain.[11–20] Research has demonstrated that these differences may be related to aspects of the low back pain experience.[21–23]

Interventions designed to target the CNS (termed herein, psychophysical interventions) have been developed and tested in a number of small studies.[24–27] Further research has combined these new interventions with traditional interventions directed towards functioning of the back, or psychological aspects of the pain experience. These data suggest that there may be additional benefit from a combined approach.[28–32] Work is underway to evaluate these treatment programs in adequately powered, prospectively registered, randomised controlled trials.[33–35]

Aim

The aim of the RESOLVE Trial is to evaluate the effectiveness of a psychophysical-traditional intervention (graded sensory-motor precision training) compared to a sham intervention for reducing pain intensity for people with persistent low back pain at 18-weeks post-randomisation. This statistical analysis plan reports the planned analyses of primary and secondary outcomes.

Study Methods

Trial design

The RESOLVE Trial is a two-group, parallel, randomised clinical trial with 1:1 allocation. Participants and outcome assessors are blinded to group allocation and study hypotheses.[33]

Eligibility

We defined these eligibility criteria in the trial protocol:[33]

Inclusion Criteria: A primary complaint of pain in the area between the 12th rib and buttock crease with or without accompanying non-radicular leg pain; episode of persistent low back pain of at least 12 weeks duration; a mean pain intensity on a numerical rating scale (NRS) ≥ 3/10 in the past week; sufficient fluency in the English language to understand and respond to English language questionnaires and engage with the intervention; access to/availability of a person who is able to assist with part of the intervention at home; access to the internet; aged 18-70. *Exclusion Criteria*: Known or suspected serious spinal pathology (fracture; malignant, inflammatory or infective diseases of the spine; cauda equina syndrome or widespread neurological disorder); suspected or confirmed pregnancy or less than six months post-partum; suspected radicular pain (dominant leg pain, positive neural tissue provocation tests and/or any two of altered strength, reflexes or sensation for the same nerve root, assessed clinically); spinal surgery

< 12 months previously; scheduled for major surgery during the treatment or follow-up period; uncontrolled mental health condition that precludes successful participation; any contraindications to transcranial direct current stimulation, cranial electrical stimulation, pulsed electromagnetic energy or low-intensity laser therapy.

(Text re-used from,[33] without amendment, under CC BY-NC-ND 4.0)

Randomisation

A scientist with no involvement in the conduct of the trial used a blocked randomisation model to generate the allocation sequence. The allocations were printed and placed in 276 sealed, opaque, sequentially numbered envelopes.[33]

Timing of outcome assessments, interim analyses and stopping guidance

The outcome measures are defined in the trial protocol. Outcomes were to be measured at baseline and 18, 26 and 52-weeks post-randomisation. Intervention credibility was measured at baseline and 2-weeks post-randomisation. We did not specify interim analyses in the trial protocol.[33]

We determined during the trial that we had sufficient funding to complete recruitment and collect the primary end-point at 18-weeks for all participants, after which we would close the trial. We collected the primary end-point for participant ID276 on 28th November 2019 and initiated the final collection of outcome data for all remaining participants that had not completed follow-up (defined as receipt of outcome data for the 52-week time point). We contacted n=45 participants to provide their 52-week time point data early and n=34 participants to provide their 26-week time point data early. This latter group of participants did not provide outcome data for the 52-week time point.

Sample size

The required sample size is n=276 participants to have at least 80% power to detect a minimal clinically important difference[36] of 1-point (SD 2.0) in pain intensity (0-10 numeric rating scale, NRS), between levels of intervention, at 18-weeks post-randomisation. We calculated the sample size for an interaction between time (four observations) and levels of intervention, using an estimated inter-observation correlation of base 0.6 with decay rate 0.1 and adjusted for up to 15% loss to follow up.[33,37]

Follow-up and withdrawal

We will use the data items depicted in Table 1 to describe the sample at baseline. We will present the sample and group measures, with a measure of central tendency and variability, for each item. We will use an adapted CONSORT flow diagram[38] and accompanying table to describe the movement of participants through the study. A shell of the adapted flow diagram is shown in Figure 1. Participants may withdraw from the trial intervention, fail to provide follow up data or both. Additionally, participants may withdraw their consent from the trial completely. We will report these items in the flow diagram and a separate table (Table A1).

Data integrity

We collected data from participants ID001-070 in hard copy format. These data will be entered in duplicate. Discrepancies will be resolved by consensus, with recourse to the Chief Investigator as required.

We collected data from participants ID071-276 using a custom-developed on-line system. These data do not require entry or checking.

Analytic Principles

General considerations

We will conduct the analyses respecting these principles:

* all participants will be analysed in the group to which they were allocated (intention-to-treat[39])
* all treatment effect estimates will be provided along with their associated 95% confidence intervals
* all statistical tests will be 2-sided with a nominal alpha level of .05
* P values will not be adjusted for multiplicity. However, the outcomes are clearly categorised by degree of importance[33] and no subgroup analysis will be performed.
* the null hypothesis for each outcome is that there is no difference between the intervention groups. Whereas, the alternative hypothesis is that graded sensory-motor precision training is superior to the control intervention.
* all analyses will be performed using STATA[40] and R.[41–43]

Outcome definitions

Primary outcome:
The primary outcome is pain intensity, defined as average pain intensity in the past week, assessed using a subject-rated 11-point NRS at 18-weeks post-randomisation.[33] The numeric rating scale is a continuous measure that ranges from 0 (no pain) to 10 (worst pain imaginable).[44]

Secondary outcomes:
The secondary outcomes are function, quality of life (QoL), recovery, adverse effects, serious adverse effects, global perceived effect (GPE) and intervention credibility.

* Function is defined as back-specific function, assessed using the Roland-Morris Disability Questionnaire (RMDQ). The RMDQ is a continuous measure, ranging from 0 (no problems with function) to 24 (severe problems).[45]
* QoL is defined as self-rated health-related QoL, assessed using the EQ-5D-5L. The EQ-5D-5L includes a 5-dimension, 5-level ordinal questionnaire and visual analogue scale with anchors "worst health you can imagine" and "best health you can imagine."[46,47]
* Recovery is defined as recovery from back pain at 26-weeks post-randomisation. We will consider a participant recovered at 26-weeks when the outcome score for pain intensity (in the past week) is either 0 or 1 on the 11-point NRS at both 18- and 26-weeks.[48–50]
* We are collecting data on adverse effects using passive capture,[44] throughout the trial period (0-52wks for each participant).[33] We will report adverse effects using the FDA definitions,[51] wherein 'any untoward medical occurrence associated with the intervention, whether or not considered related to the intervention'(edited) constitutes an adverse effect and a serious adverse effect is considered to have occurred when any of the following sequelae occur or medical intervention is required to prevent occurrence: 'death, threat to life, in-patient hospitalization or prolongation of existing hospitalisation, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions'.
* The global perceived effect of intervention is assessed using the Global Back Recovery Scale (GBRS). The GBRS is continuous, ranging from -5 (very much worse), through 0 (no different) to 5 (completely recovered, compared to the start of the treatment program).[52]

* Intervention credibility is assessed using the Credibility and Expectancy Questionnaire (CEQ). The CEQ is a continuous scale.[53]

Compliance with the intervention

Compliance was assessed by recording the attendance of participants at each treatment session. We will consider compliance as a continuous variable, defined as the number of treatment sessions attended, and as a binary variable, defined as attendance of greater than or equal to eight treatment sessions (75% of the intervention). We will present frequency distributions for both groups to describe the proportion of participants that attended each intervention session. We will also present the proportion of participants in either group that attended greater than or equal to eight treatment sessions.

Analysis

Primary outcome

We will use a mixed-effects model to estimate the effect of allocation to intervention group on the primary outcome; pain intensity at 18-weeks post randomisation. Mixed-effect models are recommended for estimating treatment effects at specific time-points in clinical trials.[54–56] We will model intervention group as a binary variable and time as a categorical variable with 4 levels corresponding to the repeated measures. We will use an unconstrained correlation structure as this is most plausible, given the repeated measurements are at different time intervals. The model will include three fixed-effect terms for the group.time interactions and a random intercept. The intercept term will account for the dependency of observations within participants due to repeated measures. The model is

$$y(ij) = \beta 0i + \beta 1.group + \beta 2.t1 + \beta 3.t2 + \beta 4.t3 + \beta 5.t1.group + \beta 6.t2.group + \beta 7.t3.group$$

, where:
* $y(ij)$ is the outcome for the i'th participant at the j'th time point,
* $\beta 0i$ is the intercept for the i'th participant, modelled as a random effect, ~N($\beta' 0i$, var($\beta 0$))
* $t1, t2, t3$ are indicator variables for the three post-randomisation time-points. Baseline is the reference time.

The primary analysis will use the point estimate of $\beta 5$ and its 95% confidence interval to estimate the effect of intervention at 18-weeks post-randomisation (Table 2).

Secondary outcomes

We will also use mixed-effects models to estimate the effect of allocation to intervention group on function, QoL and GPE. These models will be specified in the same manner as for the primary outcome. We will use appropriate coefficients and their 95% confidence intervals to estimate the effects of intervention at each follow-up time point (Table 3).
We will calculate the proportion of participants in each group that meet the definition of recovery and compare these proportions using a Chi^2 Test, or Fisher's Exact test where appropriate (Table 3).
We will compare the mean group scores for the CEQ at baseline and at 2-wks post-randomisation using an independent samples t-test (Table 3).

Adverse effects and serious adverse effects

We will display lists of all adverse effects and serious adverse effects reported throughout the trial period (0-52wks: available data for each participant) and the proportion of participants in either group that experienced them (Table A3).
We will calculate the proportion of participants that experienced any adverse effect or any serious adverse effect and compare these proportions using a Chi^2 Test, or Fisher's Exact test where appropriate (Table 3).
We will compare the proportion of adverse effects and serious adverse effects between groups using logistic mixed-effects models, provided there are a sufficient number of observations. The models will be otherwise specified as above. We will use appropriate coefficients and their 95% confidence intervals to estimate the effects of intervention at each time point (Table 3).

Estimating treatment effect with incomplete adherence

If there is significant non-adherence with the allocated interventions we will estimate the complier-average causal effect (CACE) using instrumental variable estimation.[57–59] We will also estimate the average treatment effect in the treated (ATET) using propensity score weighting.[60,61]

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Tables

Table 1. Baseline Characteristics (shell)

Characteristic	Intervention, number, central tendency (variability)	Control, number, central tendency (variability)	All participants, number, central tendency (variability)
.	n=xx	n=xx	n=xx
Age[1]	xx (xx)	xx (xx)	xx (xx)
Biological sex (female)[2]	xx (xx%)	xx (xx%)	xx (xx%)
Duration current episode LBP[1]	xx (xx)	xx (xx)	xx (xx)
Number of previous episodes LBP[3]	n=xx	xx	xx
Number of other areas of pain[3]	n=xx	xx	xx
Work absence or reduced hours[2]	xx (xx%)	xx (xx%)	xx (xx%)
Compensation claimed[2]	xx (xx%)	xx (xx%)	xx (xx%)
Highest education level			
High school year 10[2]	xx (xx%)	xx (xx%)	xx (xx%)
High school year 12[2]	xx (xx%)	xx (xx%)	xx (xx%)
Vocational certificate[2]	xx (xx%)	xx (xx%)	xx (xx%)
Diploma[2]	xx (xx%)	xx (xx%)	xx (xx%)
Bachelor degree or higher[2]	xx (xx%)	xx (xx%)	xx (xx%)
Pain intensity in the past week[1]	xx (xx)	xx (xx)	xx (xx)
Back-specific function[1]	xx (xx)	xx (xx)	xx (xx)
Self-rated health-related quality of life[1]	xx (xx)	xx (xx)	xx (xx)

1: Number, mean, standard deviation
2: Number, percentage
3: Number, median, interquartile range

Table 2. Analysis of primary outcome (shell)

Time point	Intervention, number, mean (SD)	Control, number, mean (SD)	Mean difference (95% CI)	P Value
Pain intensity at	n=xx	n=xx		
18 wks[a]	xx (xx)	xx (xx)	xx (xx to xx)	.xx
26 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
52 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall intervention effect[b]				.xx

a, b: P values are from a mixed effects model comparing between group differences at 18-weeks post-randomisation (a: primary outcome) and over the entire 52-week trial (b).

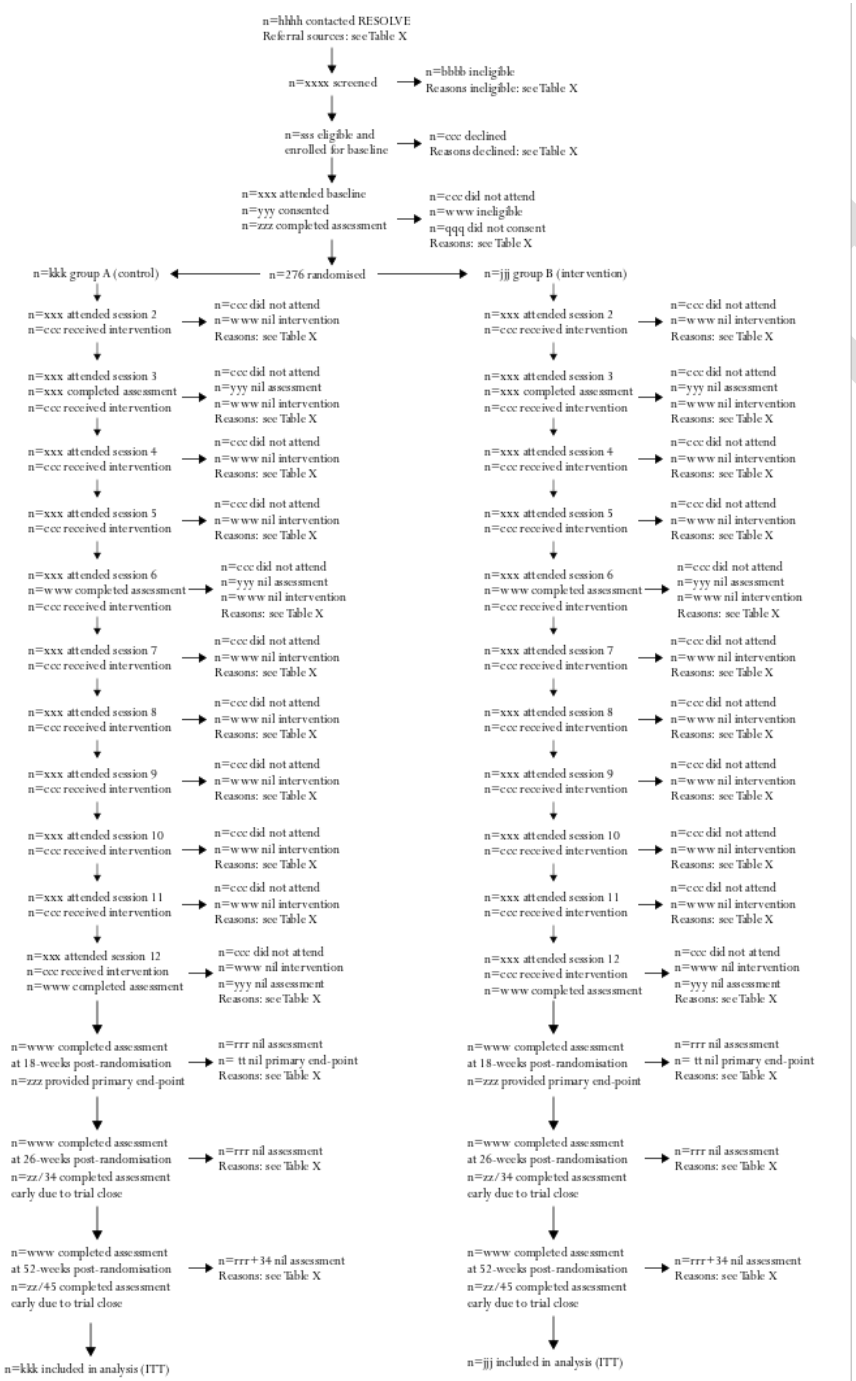
Table 3. Analysis of secondary outcomes (shell)

Time point	Intervention, number, central tendency (variability)	Control, number, central tendency (variability)	Effect measure (95% CI)	P Value
Back-specific function[a] at	n=xx	n=xx		
18 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
26 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
52 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall intervention effect[b]				.xx
Self-rated health-related QoL[c] at	n=xx	n=xx		
18 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
26 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
52 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall intervention effect[b]				.xx
Recovery[d] at	n=xx	n=xx		
26 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Adverse effects during intervention[e]	n=xx	n=xx		
18 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Adverse effects throughout trial[f]	n=xx	n=xx		
18 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
26 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
52 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall intervention effect[b]				.xx
Serious adverse effects during intervention[g]	n=xx	n=xx		
18 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Serious adverse effects throughout trial[h]	n=xx	n=xx		
18 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
26 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
52 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall intervention effect[b]				.xx
Global perceived effect[i] at	n=xx	n=xx		
18 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
26 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
52 wks	xx (xx)	xx (xx)	xx (xx to xx)	.xx
Overall intervention effect[b]				.xx

a: Roland-Morris Disability Questionnaire
b: P Value is from a mixed effects model, comparing between-group differences over the entire 52-week trial.
c: Health-related quality of life
d: A participant is considered recovered when the outcome score for pain intensity (in the past week) is either 0 or 1 on the 11-point NRS at both 18- and 26-weeks
e: Sum of any adverse effects during intervention period
f: Any adverse effects over the entire 52-week trial.
g: Sum of any serious adverse effects during intervention period
h: Any serious adverse effects over the entire 52-week trial.
i: Global Back Recovery Scale

Figures

Figure 1. CONSORT flow diagram (shell, greyscale)



Appendix

Table A1. Withdrawals (shell)

Num	Withdrew at…	Reason withdrew	Type of withdrawal
1	xx	xx	e.g. withdrew consent
2	xx	xx	e.g. stopped intervention early, provided data at follow-up
…	xx	xx	e.g. stopped intervention early, lost to follow-up
…	xx	xx	e.g. completed intervention, lost to follow-up
n	xx	xx	xx

Table A2. List of all adverse effects reported during the trial (shell)

Description	Intervention, number	Control, number	Severity	Related to trial
xx	xx	xx	xx	xx
xx	xx	xx	xx	xx
xx	xx	xx	xx	xx

Table A3. Adherence to SAP Reporting Guideline [a]

Item	Sub-item	Index	Location reported
Title	.	1a	Title
Trial registration	.	1b	Abstract
SAP version	.	2	Abstract
Protocol version	.	3	Abstract
SAP revisions	.	4a-c	Not applicable
Roles	.	5	Title page
Signatures	.	6a-c	Not applicable
Background	.	7	Introduction
Objectives	.	8	Introduction
Trial design	.	9	Methods, trial design
Randomisation	.	10	Methods, randomisation
Sample size	.	11	Methods, sample size
Framework	.	12	Analytic principles, general considerations
Interim analyses & stopping guidance	Interim analyses	13a	Methods, timing of outcome assessments…
.	Adjustment for multiplicity	13b	not applicable
.	Stopping guidelines	13c	not applicable
Timing of final analysis	.	14	Methods, timing of outcome assessments…
Timing of outcome assessments	.	15	Methods, timing of outcome assessments…
Confidence intervals & P values	Level of significance	16	Analytic principles, general considerations
.	Adjustment for multiplicity	17	Analytic principles, general considerations
.	Confidence intervals	18	Analytic principles, general considerations
Adherence & protocol deviations	Definition of adherence	19a	Analytic principles, compliance
.	Presentation	19b	Analytic principles, compliance
.	Definition of protocol deviation	19c	Not applicable
.	Presentation	19d	Protocol deviations will be reported in the final manuscript
Analysis populations	.	20	Analytic principles, general considerations
Screening data	.	21	Figure 1
Eligibility	.	22	Methods, eligibility
Recruitment	.	23	Methods, follow-up and withdrawal & Figure 1
Withdrawal/follow-up	Level	24a	Methods, follow-up and withdrawal
.	Timing	24b	Figure 1
.	Presentation	24c	Table A1
Baseline characteristics	.	25a, b	Methods, follow-up and withdrawal & Table 1
Outcome definitions	Outcomes and timings	26a	Analytic principles, outcome definitions
.	Measures and units	26b	Analytic principles, outcome definitions
.	Transformations	26c	Analytic principles, outcome definitions
Analysis methods	Methods and presentation	27a	Analysis & Tables 2 and 3

.	Adjustment for covariates	27b	None planned
.	Assessment of assumptions	27c	Analysis
.	Alternative methods	27d	Analysis
.	Adjustment for covariates	27e	None planned
.	Adjustment for covariates	27f	None planned
Missing data	.	28	Analysis
Additional analyses	.	29	Analysis, estimating treatment effect with incomplete adherence
.	Summary of safety data	30	Analysis, adverse effects and serious adverse effects & Table A2
Statistical software	.	31	Analytic principles, general considerations
References	Non-standard statistical methods	32a	Analysis & References
.	Data-management plan	32b	Not applicable
.	Trial master file	32c	Not applicable
.	Other documents	32d	Not applicable

a: Gamble et al. (2017) *JAMA* doi: 10.1001/jama.2017.18556